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ORIGINAL RESEARCH

COMPARISON OF PATELLA ALIGNMENT AND CARTILAGE BIOMARKERS IN YOUNG ADULT FEMALES WITH AND WITHOUT PATELLOFEMORAL PAIN: A PILOT STUDY

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ABSTRACT

Background: **Evidence suggests that individuals with patellofemoral pain (PFP) may develop patellofemoral joint osteoarthritis (PFJOA).** Limited data exist regarding an absolute association between PFP and PFJOA. Understanding this relationship will support the need for early interventions to manage PFP.

Hypothesis/Purpose: This study was conducted to determine if females with PFP have a patella position and cartilage biomarkers similar to individuals with PFJOA. It was hypothesized that females with PFP and excessive patella lateralization would have higher cartilage biomarker levels than controls. It also was hypothesized that a significant association would exist between pain and cartilage biomarker levels in subjects with excessive patella lateralization.

Study Design: Single-occasion, cross-sectional, observational

Methods: Pain was assessed using a 10-cm visual analog scale (VAS) for activity pain over the previous week. Patella offset position (RAB angle) was measured using diagnostic ultrasound. Urine was collected and cartilage biomarkers quantified by analyzing C-telopeptide fragments of type II collagen (uCTX-II). Independent *t*-tests were used to determine between-group differences for RAB angle and uCTX-II. Bivariate correlations were used to determine associations between VAS and uCTX-II for females with PFP.

Results: Subjects (age range 20 to 30 years) had similar RAB angles ($p = 0.21$) and uCTX-II ($p = 0.91$). A significant association only existed between VAS scores and uCTX-II for females with PFP who had a RAB angle $> 13^{\circ}$ ($r = 0.86$; $p = 0.003$). Comparison of uCTX-II in the 25-to-30-year-old females with PFP and excessive patella lateralization in the current study to published normative data showed that this cohort had elevated biomarkers.

Conclusion: These findings support that a certain cohort of individuals with PFP have features similar to individuals with confirmed PFJOA (patella lateralization and elevated biomarkers). Additional studies are needed to determine if interventions can reverse not only pain but biomarker levels.

Keywords: Knee; patella; ultrasound imaging

Level of Evidence: 2b (diagnosis)

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INTRODUCTION

Patellofemoral pain (PFP) is one of the most common knee conditions experienced by young, active females.[1] Although thought to be a self-limiting problem, emerging evidence supports an association between PFP in early adulthood and patellofemoral joint osteoarthritis (PFJOA) onset later in life.[2-5] PFJOA features include a laterally-positioned patella, patellofemoral joint space narrowing, and elevated cartilage biomarker levels.[2,6-9] Moreover, individuals with PFP have increased patellofemoral joint stress profiles (e.g., elevated bone water content, increased hydrostatic pressure, decreased patellar cartilage thickness, elevated bone metabolic activity) that may lead to degenerative joint changes.[10-13]

Degenerative changes oftentimes are not diagnosed until joint damage is evident on imaging.[14] More concerning is that these changes may occur over 20 years prior to an individual becoming symptomatic.[15] This trend supports the use of biomarkers to identify early osteoarthritic changes and joint damage.[8,16] C-telopeptide fragments of type II collagen (CTX-II) represents a cartilage biomarker typically used to monitor knee joint damage and pain and is easily collected via a urine sample (uCTX-II).[6,7,16,17] Determining if young, adult females with PFP have elevated levels of uCTX-II will provide additional evidence for an association between PFP and PFJOA.[18]

PFP is a multi-factorial problem, which has led to classification schemes to direct treatment.[19] One treatment category is patella malalignment, described as increased patella lateralization within the femoral trochlea.[19] Increased patella stress occurs as patellofemoral joint reaction forces are directed more to the lateral patella facet, a pattern that can adversely affect articular cartilage.[9] A subset of individuals with PFP have patella malalignment, a similar feature associated with PFJOA,[5] that may lead to pain and elevated uCTX-II (Figure 1).

Researchers recommend quantifying patella alignment using radiographs, computed tomography, or magnetic resonance imaging.[19] Limitations with these techniques include excessive cost, limited availability, and/or unnecessary radiation exposure. Alternatively, clinicians may use diagnostic ultrasound (US), a cost-efficient, safe, and readily available imaging tool conducive for a clinical setting.[20] Anillo et al[21] are the only ones to assess patella alignment with US. They measured a patella offset angle (RAB angle); a 13° or higher RAB angle represented excessive patella lateralization. US may represent a viable imaging modality that clinicians can use to identify patients with patella lateralization.

A certain cohort of individuals with PFP may have excessive patella lateralization and elevated uCTX-II levels. Early detection of uCTX-II may allow for early implementation of interventions designed to address impairments to prevent and/or slow disease progression.[5,18,22] The purpose of this study was to determine if females with PFP have a patella position and cartilage biomarkers similar to individuals with PFJOA. It was hypothesized that 1) those with PFP would have higher uCTX-II levels and RAB angles than controls and 2) a moderate-to-good correlation ($r > .50$) would exist between pain and uCTX-II in subjects with PFP and a RAB angle > 13°.

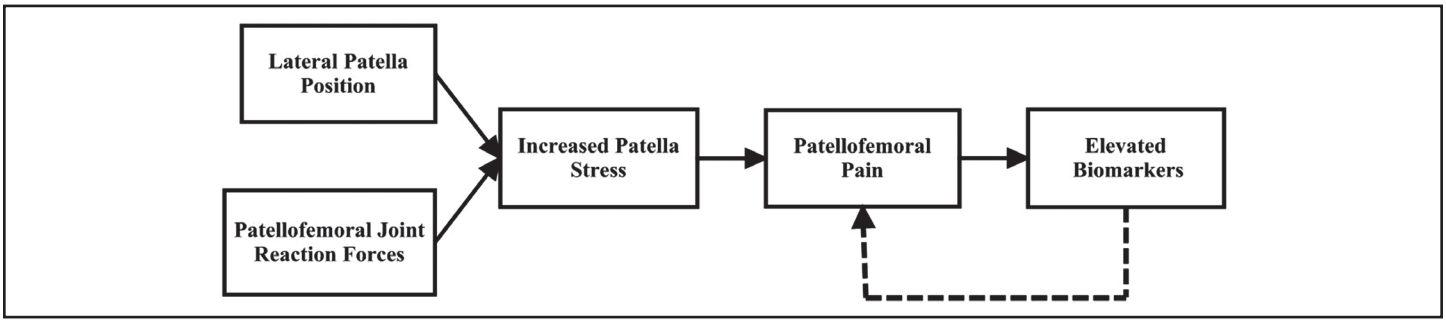

Figure 1. *Theoretical framework for the interrelationship between patella position, patellofemoral pain, and cartilage biomarker levels.*

METHODS

Study Design

A single-occasion, cross-sectional study design was used. The independent measure was group (females with PFP and controls). Dependent measures were self-reported pain, patella position, and cartilage biomarker levels.

Subjects

Eighteen healthy, recreationally active females with PFP (average age 24.7 ± 3.4 y) and 12 controls (average age 24.3 ± 1.1 y) participated. Males were excluded because of the higher prevalence of PFP in females[1,23] and naturally-occurring sex differences in uCTX-II levels.[24] A sample of convenience was recruited from a local university setting. Inclusion and exclusion criteria for subjects with PFP were based on prior investigations (Table 1).[23] The most affected extremity was tested for subjects with PFP (six subjects reported bilateral symptoms).[25] Controls participated if they were recreationally active (e.g., exercised at least 30 min, three days a week over the prior six months), had no history of PFP, and met none of the exclusion criteria (Table 1). The right lower extremity was tested for controls.[26] The investigators explained the benefits and risks of this study to all participants. The University's Institutional Review Board approved the study protocol; all subjects signed an approved informed consent document prior to participation.

Pain Assessment

Pain was assessed using a 10-cm VAS. The extreme left side of the VAS stated "no pain" whereas the extreme right side stated "worse pain imaginable." Subjects drew a perpendicular line on the scale at the position that best described their pain during activity over the previous week. The distance from the left side (e.g. no pain) of the VAS to the vertical mark made by the subject was measured to the nearest 1/10th of a centimeter and used for statistical analysis. The VAS for pain during activity over the prior week has represented a reliable, responsive, and valid instrument for assessing pain in individuals with PFP.[27]

Table 1. *Inclusion and exclusion criteria for females with patellofemoral pain.*

Inclusion Criteria *(must meet 3 of the 5 and be recreationally active)*
Visual analog rating during activity over the previous week at a minimum of a 3 on a 10-cm visual analog scale Insidious onset of symptoms unrelated to trauma for at least four weeks Anterior knee pain during at least three of the following: ○ *During or after activity* ○ *Prolonged sitting* ○ *Stair ascent or descent* ○ *During squatting* Pain with palpation of the patellar facets or pain during a step-down from a 20-cm box or double-legged squat Recreationally-active (exercise at least 30 minutes a day, three times a week for the prior six months)
Exclusion Criteria
Meniscal or other intra-articular pathology Cruciate or collateral ligament laxity Patellar tendon, iliotibial band, or pes anserine tenderness Positive patellar apprehension sign Evidence of knee effusion Hip or lumbar referred pain History of recurrent patellar subluxation or dislocation History of knee joint surgery Pregnancy

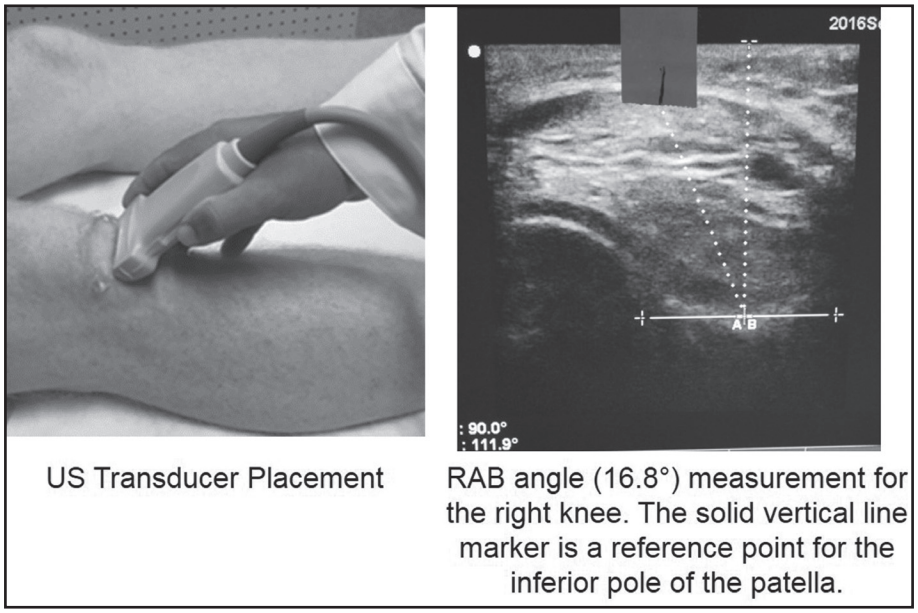

Figure 2. *Patella offset (RAB) angle measure. The RAB angle is formed by drawing a vertical line perpendicular to the lowest aspect of the femoral trochlea (i.e., representing midline) and another from the lowest aspect of the femoral trochlea to the center of the inferior pole of the patella.*

Patella Position

Patella position was quantified using US to measure the RAB angle (Figure 2), a measure similar to a patella offset angle.[21] The RAB angle was formed by drawing a vertical line perpendicular to the lowest aspect of the femoral trochlea and another from the lowest aspect of the femoral trochlea to the inferior pole of the patella. This measure has excellent inter-rater ($ICC_{2,2}$ = 0.97; SEM = 4.2˚) reliability for the two experienced physicians who measured the RAB angle (four subjects for a total of eight knees).

For testing, subjects were positioned in supine with the quadriceps relaxed and the lower extremity in a neutral position. One physician took two measures of the test knee; each examiner was blinded to the subject's group assignment. All RAB angles were recorded to the nearest $1/10^{th}$ of a degree; the average of two measures was used for statistical analysis.

uCTX-II Analysis

An early morning, second void urine sample[28] was collected, immediately processed, and stored at -70˚C until analysis. An experienced clinical laboratory scientist, who was blinded to group assignment, analyzed all data using a commercially available enzyme-linked immunosorbent assay (ELISA) based on a mouse monoclonal antibody raised against the EKGPDP sequence of human CTX-II (Urine CartiLaps® EIA; Immunodiagnostic Systems; Gaithersburg, MD). CTX-II was corrected for urinary creatinine concentration using the following formula: corrected CTX-II (ng/mmol) = [1000 X Urine CartiLaps (ng/ml)]/ creatinine (mmol/L). uCTX-II levels were log-transformed (ln uCTX-II) to minimize the influence of outliers and used for statistical analysis.[28]

Statistical Analysis

Separate independent student's *t*-tests were used to determine differences for age, mass, height, RAB angle, and ln uCTX-II in females with and without PFP. Bivariate correlations were conducted to determine associations between VAS scores and ln uCTX-II for all subjects with PFP. For this purpose, separate bivariate correlations were conducted for all subjects with PFP, those with a RAB angle $\leq$ 13˚, and those with a RAB angle > 13˚. Correlation coefficients (*r*) were interpreted as follows:[29] none less than 0.25; fair between 0.25 and 0.50; moderate-to-good between 0.50 and 0.75; and good-to-excellent over 0.75. All analyses were conducted using SYSTAT 13.0 (Systat Software, Inc., San Jose, CA) at the 0.05 level of significance.

Table 2. *Mean ± (standard deviation) of demographic data for females with patellofemoral pain (PFP) and controls.*

Variable	PFP	Controls	*p*-value
Age (y)	24.7 (3.4)	24.3 (1.1)	0.59
Mass (kg)	69.8 (16.3)	65.5 (13.3)	0.45
Height (cm)	168.4 (8.0)	167.6 (10.4)	0.83

Table 3. *Mean ± (standard deviation) and 95% confidence interval (95% CI) for patella position (RAB angle) and cartilage biomarker levels (uCTX-II) for all females with patellofemoral pain (PFP) and controls.*

Variable	PFP N = 18	Controls N = 12	*p*-value
RAB Angle*	10.7 (11.2) (95% CI, 4.6-17.2)	5.9 (7.9) (95% CI, 1.0-11.0)	0.21
uCTX-II†	5.9 (0.8) (95% CI, 5.4-6.4)	5.9 (0.6) (95% CI, 5.5-6.3)	0.91

* RAB angle measured to the nearest 1/10th degree
† Log-transformed uCTX-II level reported in ng/mmol

RESULTS

Subjects with and without PFP were similar with respect to age, mass, and height (Table 2). Subjects with PFP had average VAS scores of 3.7 ± 1.7 cm and controls were pain-free. Females with PFP exhibited a 1.8 times greater RAB angle than controls (Table 3). Associations between VAS scores and ln uCTX-II were not significant when analyzing all females with PFP (r = 0.02; p = 0.94) and those with a RAB angle ≤ 13° (r = -0.36; p = 0.35). However, a significant association (r = 0.86; p = 0.003) existed for those with a RAB angle > 13° (Figure 3).

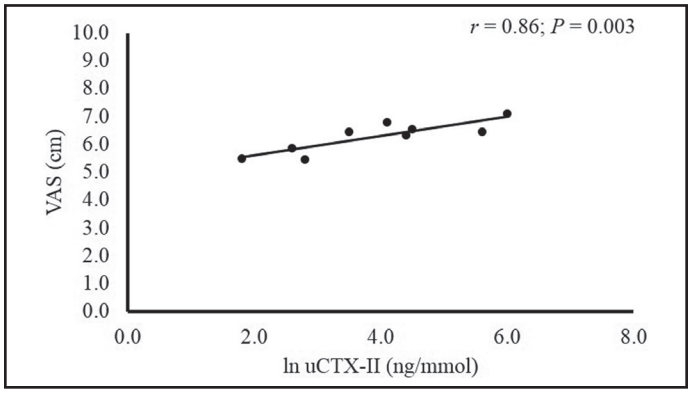

Figure 3. *Correlation between visual analog scale (VAS) scores and log-transformed urinary C-telopeptide fragments of type II collagen (ln uCTX-II) in females with patellofemoral pain exhibiting excessive patella lateralization.*

DISCUSSION

The purpose of this study was to determine if females with PFP have a patella position and cartilage biomarkers similar to individuals with PFJOA. It was hypothesized that 1) those with PFP would have higher uCTX-II levels and RAB angles than controls and 2) a moderate-to-good correlation (r > .50) would exist between pain and uCTX-II in subjects with PFP and a RAB angle > 13°.

No significant between-group differences were shown with respect to biomarkers or patella position. However, a good-to-excellent correlation existed between pain and biomarkers for subjects with PFP and excessive patella lateralization.

Patella Position in Females with and without PFP

Although the RAB angle for females with PFP was 1.8 times greater than controls, this difference was not significant. The post-hoc power analysis showed that 65 females with and without PFP were required to attain 80% power. Although the imaging technique had excellent inter-rater measurement reliability, the measure's inherent variability most likely precluded obtaining statistical significance. Additional larger-scale studies are needed to determine if

females with PFP have increased patella lateralization than controls.

Fifty percent of females with PFP exhibited a high RAB angle (18.6° ± 10.9°) while the remaining 50% did not (2.8° ± 3.0°). This pattern suggested that impairments other than static patella position may have existed.[18] Faulty lower extremity kinematics like excessive hip adduction and/or internal rotation during weight bearing activities can increase lateral patellofemoral joint loading and stress.[30,31] A relative delay in vastus medialis-to-vastus lateralis activation during weight bearing activities also may lead to increased lateral loading and stress.[32] This determination could not be made since kinematic and neuromuscular factors were not assessed.

Cartilage Biomarker Levels in Females with and without PFP

Subjects with and without PFP had ln uCTX-II of 5.9 ± 0.8 ng/mmol and 5.9 ± 0.6 ng/mmol, respectively, which exceeded levels reported for individuals with confirmed early knee osteoarthritis.[6] However, comparing the current study findings to Ishijima et al[6] presented limitations because age can affect uCTX-II. Mouritzen et al[24] found naturally-higher non-log-transformed uCTX-II in healthy 20-to-24-year-old females (500 ng/mmol) than 25-to-30-year-old females (225 ng/mmol). uCTX-II continued to be lower in healthy 31-to-35-year-old females (150 ng/mmol). They concluded that the naturally-higher levels of uCTX-II seen in 20-to-24-year-old females resulted from higher bone turnover.[24]

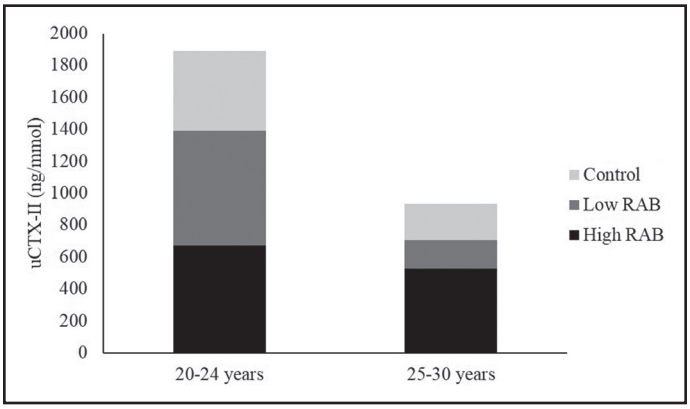

Figure 4. *Relative amount of mean non-log-transformed uCTX-II (ng/mmol) levels for females with patellofemoral pain (PFP) according to age and amount of patella lateralization (RAB) to values from a large-scale study of healthy, age-matched controls.[29] A RAB angle of 13° or higher represented a high RAB angle.[28]*

To make meaningful comparisons to Mouritzen et al,[24] data for subjects with PFP were stratified by age (20-to-24 years and 25-to-30 years), expressed as non-log-transformed uCTX-II, and averaged (Figure 4). Average non-log-transformed uCTX-II for the 20-to-24-year-old subjects, regardless of RAB angle, were similar to previously reported values from Mouritzen et al.[24] This finding suggested that these females with PFP had naturally-higher uCTX-II consistent with their age group regardless of patella position.

Meaningful differences existed when making the same comparison for 25-to-30-year-old females. Females in this age range with PFP and a higher RAB angle had non-log-transformed uCTX-II (525.8 ng/mmol) that was 2.2 times higher than healthy, age-matched females (225 ng/mmol).[24] This difference indicated that this subgroup of females with PFP had higher than expected uCTX-II for their age range. Therefore, differences in uCTX-II based on patella position may not necessarily be clinically meaningful until naturally occurring bone turnover ceases. Additional studies are needed to make this determination.

Associations between Pain and Cartilage Biomarker Levels based on Patella Position

No significant association was found between VAS and ln uCTX-II when analyzing all females with PFP, regardless of patella position, and those with a RAB angle ≤ 13°. However, a good-to-excellent correlation existed for females with PFP classified as having excessive patella lateralization (Figure 3). This finding, plus the fact that these subjects had elevated biomarkers than reported normative data,[24] suggested that at least a cohort of females with PFP had similar features (e.g., patella lateralization and elevated biomarkers) as individuals with confirmed PFJOA.[2,6,9]

Implications for Rehabilitation

PFP is no longer considered a self-limiting problem but a disease process.[18,22,33,34] Study findings support this belief since 25-to-30-year old females with PFP and excessive patella lateralization had elevated biomarkers, which could suggest cartilage degradation.[6,24] These results further highlight the importance of early management of females with PFP.[22]

A challenge with the management of PFP is its multifactorial nature and the need for identifying treatment classifications for this patient population.[19,35] While therapeutic exercise remains the recommended treatment strategy,[36] the addition of patella taping can provide short-term benefit for individuals with PFP[36] and PFJOA.[37] This investigation supports the use of US to identify females with PFP and excessive patella lateralization. This finding may be useful in identifying females with PFP who may benefit from patella taping. However, additional studies are needed to make this determination.

Delimitations

Study findings cannot be extrapolated to males with PFP since only females were examined. Males were excluded because of naturally-lower uCTX-II than healthy, age-matched females.[24] PFP also is more prevalent in females,[1] and males with PFP may have different impairments.[25]

Another delimitation was the procedure used to measure patella position. Measuring static patella position with subjects in supine and the quadriceps relaxed most likely did not represent functional demands. Some subjects may have demonstrated greater patella lateralization if positioned in either supine or standing with the quadriceps contracted. Pilot testing showed unacceptable measurement reliability when measuring in supine and standing with the quadriceps contracted. Therefore, all subjects with excessive patella lateralization may not have necessarily been identified.

Finally, the current study was a pilot project to examine the interrelationship between patella position and biomarkers. For this reason, only uCTX-II was assessed since it represented the most commonly used biomarker to identify and monitor knee degenerative changes.[8,16] However, use of a single biomarker probably did not adequately characterize cartilage pathophysiology.[38] Future studies should examine a cluster of cartilage degradation and cartilage synthesis biomarkers in this subject cohort.[39]

Limitations

This study has additional limitations. uCTX-II has been used to identify and monitor knee osteoarthritis.[7] However, it was a byproduct of cartilage degradation that only provided an indirect assessment of joint damage. uCTX-II lacked the ability to distinguish between PFJOA and TFOA. However, PFJOA has been considered a risk factor for not only TFOA onset but progression.[33] Poole et al[15] concluded that individuals with knee OA can undergo degenerative changes over 20 years prior to becoming symptomatic. Biomarkers may provide a way for early detection of degenerative changes and further support the importance of rehabilitation for females with PFP.[22] Radiographs were not taken, precluding the ability to know if subjects with PFP and elevated uCTX-II had cartilage changes to the tibiofemoral, patellofemoral, or both joints. However, inclusion criteria were consistent with prior works[23] intended to exclude subjects with evident degenerative changes. Also, one-third of subjects with PFP had bilateral symptoms and it was unknown if this presentation affected uCTX-II levels. Finally, uCTX-II typically was higher in females between the ages of 20-to-24 years due high bone turnover.[24] Using more sensitive measures of cartilage biomarkers (e.g., serum or synovial fluid samples) may have identified differences in this cohort.

CONCLUSION

This study was the first to compare patella position and cartilage biomarkers in young, adult females with and without PFP. While no significant differences were identified, a clinically-relevant association existed between pain and biomarkers in females with excessive patella lateralization. Moreover, 25-to-30-year old subjects with PFP and excessive patella lateralization had higher biomarker levels that exceeded both normative data and values from individuals with confirmed PFJOA.[6,24] Future studies are needed to determine the effect that an intervention can have on reducing both pain and biomarkers in this cohort of females with PFP.

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